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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/499,526	02/10/2000	Kuanghui Lu	CIBT-P01-058	1398
28120	7590	06/15/2004	EXAMINER	
ROPE & GRAY LLP ONE INTERNATIONAL PLACE BOSTON, MA 02110-2624			DEBERRY, REGINA M	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)	
	09/499,526	LU ET AL.	
	Examiner Regina M. DeBerry	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM  
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) Responsive to communication(s) filed on 24 March 2004.
- 2a) This action is FINAL.      2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 13,15-21,23,28-33,39,45,46,50,53,54,57-61,76-78,85,87-112 and 116-119 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
  1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 3/24/04.
- 4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: \_\_\_\_\_.

Continuation of Disposition of Claims: Claims pending in the application are 13,15-21, 23, 25-33, 35-37, 39, 45, 46, 50, 52-62, 65-67, 69-71 and 73-119.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 25-27, 35-37, 52, 55, 56, 62, 65-67, 69-71,73-75,79-84,86 and 113-115.

***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 24 March 2004 has been entered.

***Status of Application, Amendments and/or Claims***

The amendment filed 24 March 2004 has been entered in full.

Claims 1-12, 14, 22, 24, 34, 38, 40-44, 47-49, 51, 63, 64, 68 and 72 were cancelled.

New claims 95-119 were added.

Claims 25-27, 35-37, 52, 55, 56, 62, 65-67, 69-71, 73-75, 79-84, 86, 113, 114 and 115 are withdrawn from consideration as being drawn to a non-elected Group. Please see original Election/Restriction requirement (14 December 2000).

Claims 13, 15-21, 23, 28-33, 39, 45, 46, 50, 53, 54, 57-61, 76-78, 85, 87-112, 116-119 are under examination.

The information disclosure statement filed 24 March 2004 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the

application file and the information referred to therein has been considered as to the merits.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 15-21, 23, 28-33, 39, 45, 46, 50, 53, 54, 57-61, 76-78, 85, 87-112 and 116-119 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to methods for:

- (1) inducing or enhancing the glucose responsiveness of pancreatic islet or cell or
- (2) inducing or enhancing glucose metabolism in an animal having a disease associated with abnormal glucose metabolism or
- (3) maintaining or restoring glucose responsivity or glucose sensing of pancreatic beta cells

comprising administering to pancreatic islet/cells or an animal or cultured pancreatic islet/cells:

(1) a PYY agonist or a biologically active fragment thereof, wherein said PYY agonist comprising a polypeptide encoded by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 X SSC at 65C to SEQ ID NO:1, or

(2) PYY or a biologically active fragment thereof, or

(3) PYY agonist or a biologically active fragment thereof, wherein said PYY agonist comprises a polypeptide with various % identities to SEQ ID NO:3.

Applicant states that given the functional limitations expressly recited in the claims, PYY variant peptides that do not retain the recited function do not fall within the scope of the claims. In reference to the Wells paper submitted by the Examiner, Applicant points out that there has been a veritable explosion in the art of combinatorial chemistry which can allow the making and testing of polypeptide variants without undue experimentation. Applicant argues that the important consideration in determining whether Applicants have enabled the use of PYY variants in the subject methods is whether one of skill in the art could make and test polypeptide variants using the techniques of the specification and the state of the art, without undue experimentation, in order to select PYY variants for use in the subject methods. Applicant contends that the specification provides a detailed description of methods of making and testing variants using combinatorial mutagenesis.

Applicant argues that the claims have been amended to provide additional functional limitations to describe the claimed subject matter. Applicant reminds the Examiner that several PYY variants have been identified and the ability of these variants to mimic one or more functions of PYY has been demonstrated. Applicant

submits that these examples demonstrate that not only could one of skill in the art make and test variants to identify those variants with particular functional attributes, but one of skill in the art did make and test variants to identify variants with particular attributes. Applicant states that Balasubramaniam *et al.* show that several PYY fragments mimic the effects of PYY *in vivo* in rat intestine. Liu *et al.* demonstrate that several PYY analogs retain the ability to bind to pancreatic cancer cells. Challis *et al.* present *in vivo* results demonstrating that PYY variants mimic the effects of PYY on food uptake and hypothalamic expression when administered intraperitoneally to mice (Exhibits 1-3 respectively).

Applicant's arguments have been fully considered but are not deemed persuasive because the references submitted by Applicant are drawn to different methods using PYY. The method claims sought to be patented are drawn to inducing or enhancing the glucose responsiveness of pancreatic islets or cells comprising administering PYY (PYY agonist, variants or biologically active fragment thereof). The submitted references fail to teach that PYY variants can induce or enhance the glucose responsiveness of pancreatic islets or cells. **Most importantly**, the instant specification teaches that *PYY increases the amount of insulin release* in response to glucose in cultured pancreatic islets (specification; pages 50-51). **However**, the prior art of record submitted by Applicant teaches that *PYY inhibits insulin secretion* stimulated by glucose (Bottcher *et al.*, Pancreas 4(3):282-8, 1989 and Bertrand *et al.*, Pancreas 7(5):595-600, 1992). This data is in direct contrast to what the instant examples demonstrate. Thus, it is unclear what working conditions are needed/required for PYY to increase insulin

release in response to glucose. The specification fails to explain this discrepancy. Furthermore, if PYY does not always increase insulin release in response to glucose, it would be **highly unpredictable** that "PYY agonists", "PYY variants", "biologically active fragments thereof", etc would increase insulin release in response to glucose. The specification would not support claims to PYY polypeptides modified to an unlimited extent relative to those exemplified. One of skill in the art could not readily make and test PYY variants without undue experimentation because the evidence suggest that PYY does not always increase insulin release in response to glucose. In light of the contradictory evidence, one skilled in the art could not readily anticipate the effects of PYY, agonist, variants or biologically active fragments thereof.

In addition, claims 23, 28, 29, 59, 60, 76, 89, 102-112, 116-119 are drawn to methods of treating a disease associated with altered glucose metabolism comprising administering to an animal having a disease associated with glucose metabolism PYY (or PYY agonist or biologically active fragment thereof). The subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure because the specification fails to teach how to treat any disease associated with altered glucose metabolism with PYY. The working examples are not tantamount to *treating a disease associated with glucose metabolism*. As the instant specification states, diseases associated with altered glucose metabolism can encompass insulin resistance, glucose intolerance or glucose non-responsiveness, hyperglycemia, obesity, hyperlipidemia and hyperlipoproteinemia. The physiological response of cells in culture does not necessarily or predictably correlate with an effect *in vivo*.

Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light. It is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in cell-cell interactions. Furthermore, the instant specification fails to teach the use of known animal models for Type II diabetes such as Zucker fa/fa rats and ob/ob mice or known Type 1 diabetes animal models such as non-obese diabetic (NOD) mice or bio-breeding (BB) rats. The *in vitro* experimental data presented in the instant specification is clearly not drawn to treating diseases associated with altered glucose metabolism in subjects.

Lastly, the specification fails to teach or submit references, which teach that exocrine or endocrine cells be glucose responsive (claims 95 and 99).

Due to the large quantity of experimentation necessary to demonstrate that PYY (PYY variants, PYY agonists or biologically active fragments thereof) can treat a disease associated with altered glucose metabolism in a subject, the lack of

direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the poor correlation between *in vitro* assays and treatments in subjects and the conflicting prior art which teaches that *PYY inhibits insulin secretion* stimulated by glucose, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

### ***Claim Objections***

Claims 13, 90, 92 and 93 are objected to because the instant claims comprise very similar steps which raise the question of similar scope (claim 13 versus claim 93 and claim 90 versus claim 92). If the claims are not of similar scope, Applicant is asked to specifically point out in the instant specification the patentable distinction between the claims.

### ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*RMD*  
RMD  
6/9/04

ELIZABETH KEMMERER  
PRIMARY EXAMINER

*Elizabeth C. Kemmerer*